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(54) Method for the treatment of ATL and the Inhalant for the same.

(57) An improved method for treating or curing ATL, with lowered side effects, comprising administering an effective amount of interferon- γ to a mammalian species in need of such treatment *via* respiratory tract by inhalation, wherein recommended is that a single dose of said interferon- γ to human adults is 1,000,000 JRU to 6,000,000 JRU and the single dose is repeated at a frequency between once-a-week and twice-a-day.

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METHOD FOR THE TREATMENT OF ATL AND THE INHALANT FOR THE SAME

The present invention provides new use of interferon- γ (hereafter referred to as IFN- γ), in particular, it relates to useful methods for the treatment of adult T cell leukemia/lymphoma (hereafter referred to as ATL), which is characterized by the new route of administration *i.e.*, inhalation. This invention also provides pharmaceutical compositions, suitable for inhalation and for the purposes above.

ATL was first described as a specific clinical entity by Takatsuki *et al.* in 1976, which has occurred frequently in Japan, especially in southern Kyushu island area. The detection and isolation of human T-lymphotropic virus type-I (hereafter referred to as HTLV-I) by Gallo and his colleagues in 1979, and the discovery of the association of the HTLV-I with ATL are expected to shed new light on human cancer study. No effective drugs have been found, nor have there been established any effective methods of treatment for ATL. Therefore, the prognosis of ATL was reported to be poor, with most patients dying within a year.

Since interferons have not only activities against various viruses but also activities against a variety of tumors, studies have been made for the treatment of ATL with intravenous administration of these. However, neither independent use of IFN nor even its use in combination with other drugs has produced satisfactory results.

It is the object of the present invention to provide a pharmaceutical composition which offers a new and effective route of administering IFN- γ to a patient in need thereof. This object has been achieved on the basis of the surprising finding that when IFN- γ is administered directly to the lungs of a mammal by means of inhalation, it becomes possible to treat ATL effectively.

The subject matter of the invention therefore is a pharmaceutical composition for the administration via the respiratory tract by inhalation containing interferon- γ (IFN- γ), which comprises combining an effective amount of IFN- γ with a physiologically acceptable vehicle for inhalation.

The pharmaceutical composition of the invention which is specifically used for treating or curing ATL is very safe with low side effects.

In the treatment of ATL, preferably 1,000,000 JRU to 6,000,000 JRU of aerosolized IFN- γ is repeatedly administered *via* the respiratory tract by inhalation at twice-a-day to weekly intervals to a mammalian species, *esp.*, human adults in need of such a treatment ("JRU" stands for Japanese Reference Unit).

The inhalant of this invention may be in a liquid form, or in a powder form, or in a crystal form. When in a liquid form, it can be supplied in ampules; and when in a powder or crystal form, it is packed in vials, which is, at the time of use, dissolved in distilled water for injection use or in physiological saline, and then administered with a nebulizer.

For the purpose of this invention, it is not particularly necessary to use any additive. However, when the product is packed in vials, and it is to be used after being dissolved, it is desirable to add to the main ingredient, namely IFN- γ , serum albumin or a surfactant, and maltose and a buffer solution, when solubility, storage stability, etc. of IFN- γ are taken into consideration.

Such a preparation is made into a solution, and administered by inhalation with the use of a nebulizer. In so doing, it is not desirable for the solution of the preparation to be extremely acidic or alkaline. Therefore, when a buffer solution is used, such buffer should be used to keep the solution practically in a neutral range. The thus prepared solution is very desirable as it seldom causes inflammation at the administration site. In this invention, it is preferable to use a phosphate buffer, and it is desirable for the buffer solution to show a buffer range of about pH 6.5 - 7.5.

Furthermore, to prevent inflammation or allergic reaction, pretreatment may be made, if necessary, with *e.g.* a steroid.

The steroid may be added to the preparation beforehand. In addition, an antibiotic can also be given parenterally or orally to prevent infection or for the purpose of treatment. It is also possible to add an aminoglycoside antibiotic to the solution for inhalation. The solubility in water of a polypeptide such as IFN- γ is low. So, for the inhalation of the therapeutically necessary amount of IFN- γ , a large amount of water is necessary, but this is not desirable for an inhalant. If the product is suspended in a small amount of water, the sprayed particles become large even with the use of a high-performance nebulizer, and consequently it becomes difficult for the drug to reach the target site. This is not desirable. On the other hand, when serum albumin is added, the solubility and storage stability of IFN- γ are improved, with the result that the drug can be dissolved completely in the minimum amount of water or physiological saline solution. Then, the aforesaid drawbacks are all solved. The solution thus prepared shows an unexpectedly good solubility, and even when the solution is left for a long time at room temperature, no turbidity takes place, and thus its stability is maintained. Nor was there seen any decrease in the potency of IFN- γ . As for serum albumin, human serum albumin is used preferably, and it can be substituted by a surfactant.

The IFN- γ used in this invention is that of natural origin or of recombinant type. What is especially preferable is recombinant human IFN- γ (hereafter referred to specifically as hIFN- γ).

The single dosage IFN- γ is about 1,000,000 to 6,000,000 JRU, preferably about 3,000,000 JRU, which is dissolved in about 5 to 30 ml of distilled water for injection use and/or physiological saline and then administered by inhalation over several minutes to several tens of minutes using a nebulizer. The inhalation is given at the frequency of once a week to once a day. For an inpatient, it is given more frequently. For an outpatient after remission, it is given once a week. Thus, the single dosage and the frequency to apply may vary, depending on the patient's symptoms or conditions.

The composition of this invention and the method of this invention are useful for even the single therapy of using IFN- γ alone. However, it may be also useful in combination with a conventional chemotherapy. It is recommended to administer inhalation in combination with a publicly-known treatment by combined use of a plural number of drugs. When necessary, radiotherapy may also be used in combination with the inhalation.

An example of the preparation of this invention is given below:

IFN- γ About 1,000,000 - 6,000,000 JRU

Human serum albumin About 0.2 - 40 mg

Maltose About 0.02 - 0.4 g

L-cystein About 0.1 - 2.0 mg

0.1 M phosphate buffer A necessary amount to make the whole 2.0 ml.

When a freeze-dried preparation is desired, a solution consisting of the above ingredients is frozen quickly at -10 to -60°C, preferably at -25 to -40°C, for several minutes to 10 and several hours. After that, if necessary, the product is kept at about 0.005 to 1 mb for about 5 to 72 hours, while supplying heat of sublimation, and thereby water is removed by sublimation so as to bring the water content down to a desired level. Then, if necessary, inert gas such as nitrogen, or dried air may be supplied in the container, which is then closed tightly. In taking the foregoing procedures, it is desirable to use a conventional method. The freeze-dried product obtained as above is completely soluble in about 1 to 2 ml of distilled water.

The following Examples and Trials serve to illustrate the practical formulations and methods of the present invention, but those are not intended to limit the scope of this invention.

Example

In a suitable quantity of 0.1 M sodium dihydrogen phosphate -disodium monohydrogen phosphate buffer, the pH of which has been adjusted to 6.8, are dissolved 7.5 x 10⁸ JRU equivalent of hIFN- γ , 1.25 g (as dry weight) of human serum albumin, 12.5 g (as dry weight) of maltose of pharmacopoeia grade, and 0.075 g of L-cysteine. To this is added the aforesaid buffer solution to bring the total volume to 500 ml, which is then filtered through a suitable membrane filter, whereby a germ-free solution is obtained. The germ-free solution is supplied in vials at 2 ml per vial. The vials are then frozen at a temperature below -25°C, and while keeping the product at a temperature below -25°C, freeze-drying is performed by a conventional method, whereby a freeze-dried preparation is obtained.

Clinical Trials

(Testing preparation)

A vial of S-6810 (freeze-dried preparation, each containing 3,000,000 JRU of hIFN- γ) furnished by Shionogi & Co., Ltd. is dissolved in 1 ml of distilled water for injection use, which is then diluted with 20 ml of physiological saline solution. The solution thus prepared was administered to the following patients by inhalation over 20 minutes with the use of an ultrasonic nebulizer. Unless otherwise indicated, the inhalation was given once daily.

(Patients receiving inhalation)

The aforesaid treatment was given to 12 patients who had been finally diagnosed as having ATL. Of these 12 patients, 6 patients (Case Nos. 1 - 6: 4 chronic type and 2 acute type) received this inhalation

therapy without any other chemotherapy, and 6 patients (Case Nos. 7 - 12: 3 acute type and 3 lymphoma type) received it together with combination chemotherapy. The combination chemotherapy regimen consisting of Cytarabine, Vincristine (or Vindesine), Cyclophosphamide, Prednisolone and Peplomycin are shown in Table.

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(Criteria for the evaluation of effect)

The effect of the treatment was evaluated based on the criteria for the evaluation of effect in the chemotherapy of cancer set by Koyama-Saito group. A complete disappearance of detectable abnormalities was rated as CR (complete response), contraction rate of 50% or more as PR (partial response), contraction rate of less than 50% and enlarging rate of less than 25% as NC (no change), and enlarging rate of 25% or more as PD (progressive disease). Three patients (case 1, 4 and 5; 2 chronic type and 1 acute type) out of 6, treated with aerosolised IFN- γ inhalation therapy alone, obtained PR (effective rate, 50 %). Four patients (case 7, 8, 10 and 12; 2 acute type and 2 lymphoma type) out of 6, treated with the combination of the aerosolised IFN- γ inhalation therapy and the chemotherapy, obtained PR (effective rate, 67 %). The response might be judged as CR in these 7 patients if abnormal lymphoid cells (ATL-like cells) on examination of blood smears disappeared. The details of each patient are given below:

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Case 1 (74 years old, female; chronic type)

This patient has a previous history of a chronic bronchitis-like respiratory disease of about 6 years. She has had fever, cough, sputum, and weight loss for these 2 months. Her doctor, pointed out hematological abnormalities and sent her to us for hospitalization. At the time of admission, there were no particular physical findings worthy of note. Her % VC was 81% and % FEV_{1.0} was 56%.

From one month after hospitalization, inhalation therapy (once a day) was started on as a diagnosis of ATL. From about one month after the start of the inhalation, marked improvement was seen in hematological findings and surface marker analysis of peripheral blood lymphocytes, and at the same time, cough and sputum abated, body weight increased, and the fever tended to abate. Thus, marked improvement was observed in her general condition. She is still receiving the treatment at 3 to 4 times a week as an outpatient and continues to show no evidence of recurrence.

Case 2 (59 years old, male; chronic type)

This patient came to us for admission because of leucocytosis with abnormal lymphocytes (ATL cells), which was picked up during a complete health examination. There was nothing noteworthy in subjective or objective symptoms, or in physical findings. With a diagnosis of ATL 3,000,000 JRU of IFN- γ was given (once a day) by intramuscular injection for 54 days. After he was discharged from the hospital, he continued to come to hospital, twice a week, to receive the treatment. From 3 months before (8 months after he was first hospitalized), inhalation therapy was started at our outpatient clinic (3 to 4 times/week). No clear improvement in hematological findings was seen throughout the treatment periods. However, there are no particular subjective or objective symptoms even at present, and the patient is leading a normal life.

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Case 3 (71 year old, male; chronic type)

This patient had had chronic bronchitis-like symptoms from time to time for several years. When he was hospitalized for dysuria at the department of urology of our hospital, he was found to have a hematological abnormality, so he was transferred to our department. Then, he was found to have prostatic hypertrophy. At the same time, the chest X-ray view and pulmonary function test showed a diffuse pan-bronchiolitis-like abnormality. After hospitalization, inhalation therapy was started. While hospitalized, he received inhalation every day for 50 days, and after discharge from hospital, he continues to receive the treatment 3 times a week. No clear improvement was observed in hematological findings, and cough and sputum persisted. Therefore the effect was rated as NC.

Case 4 (56 years old, male; chronic type)

From 3 months before, the patient began to have dry cough, a slight fever, and weight loss (4 kg/3 months). he was diagnosed by his community doctor as having malignant lymphoma and aspergillosis of the lung, and the patient was admitted to out hospital for close examinations.

Generalized superficial lymph nodes swelling, up to the size of the tip of the thumb, were palpable, and rale was noticed in the left lung. The inhalation therapy was started on with oral administration of amphotericin B syrup and a penicillin type antibiotic as a diagnosis of ATL with aspergillosis of the lung. After start of the inhalation, the fever abated soon, and improvement was also seen in his dry cough. After 2 months, the swelling of lymph nodes disappeared, OKT4/OKT8 ratio normalized, and the body weight was restored. Improvement was also observed in the abnormal shadow previously seen in the chest X-ray view. He continues to receive the therapy 3 times a week at out out-patient clinic.

Case 5 (52 years old, male; acute type)

The patient has had constipation and abdominal distention for 3 weeks. He was found, by his family doctor, to have swellings of the liver and spleen, and also leukocytosis. He was then admitted to our hospital with suspected leukemia. Initial laboratory data: WBC 40,700 (with 86.5% ATL cells); OKT4/OKT8 ratio 25.44; LDH 3,160 Wrob. U.; total bilirubin 5.2 (direct 2.7) mg/dl; and alkaline phosphatase 40.1 K.A.U.

Mild Chemotherapy was started under intensive supportive therapy as a diagnosis of ATL. However, a resistance was seen, and fever persisted, with the temperature staying at the level of 39°C. And there occurred a lymph node swelling of the size of a quail egg. Two months after hospitalization, when chemotherapy was suspended, inhalation therapy was started. Then, the lymph nodes swelling, hepatomegaly and splenomegaly disappeared, and a marked improvement was seen in all laboratory findings. OKT4/OKT8 ratio was also normalized.

No chemotherapy was made after the start of the inhalation therapy. However, subjective and objective symptoms have all disappeared, with the exception that only 5 - 10% abnormal lymphoid cells in the peripheral blood was seen. He is now back at work and having an inhalation of IFN-γ every day at his home.

Case 6 (61 years old, female; acute type)

This patient was admitted to our hospital because of left cervical lymph nodes swelling noticed 1 month ago. At the time of admission, generalized superficial lymph node swellings, up to the size of a walnut, were palpable. The patient did not respond to any drug such as YK-176 (2'-deoxycytosine <DCF>), MTX, or other combination chemotherapy. One month after every chemotherapy was suspended, when the underlying disease worsened, inhalation therapy was given every day without using any other chemotherapy. At one time, increase in LDH leveled off, and the swelling of lymph nodes tended to become smaller. However, abdominal lymph nodes swelling had become remarkable and she died after the 6 month hospitalization.

Results on Cases 1 to 6 are summarized in Table 1 and those on Cases 7 to 12 are in Table 2.

Case 7 (38 years old, female; acute type)

This patient had had chronic bronchitis-like symptoms for 8 months ago, and was referred to out hospital because of painful right cervical lymph nodes swelling and abnormal chest X-ray observation. Physical examination revealed systemic lymph nodes swelling, up to 4cm in diameter. In the generalized lung field rales could be heard. The liver and spleen were not palpated. She was diagnosed as having malignant lymphoma, diffuse, pleomorphic type (T-cell type with markers of both CD4 and CD8).

She then was started on IFN-γ inhalation therapy with combination chemotherapy (modified VDS-CAP combination chemotherapy). One month after the treatment, lymph nodes swelling markedly decreased in size, and improvement of the chest Xp view was seen. She continues to receive the treatment in the outpatient clinic and is still in PR.

Case 8 (35 years old; female; acute type)

This patient was referred to out hospital because of generalized lymph nodes swelling, cough and skin rashes. Chest Xp revealed bilateral hilar lymph nodes swelling with diffuse abnormal shadows in the all lung field. Histological examination of a lymph node biopsy specimen showed malignant lymphoma, diffuse, medium-sized cell type (T-cell type with markers of CD4, CD11 and CD25).

After diagnosis of ATL the IFN- γ inhalation therapy was started with the combinations chemotherapy with good effects. However, 6 weeks later she developed recurrence of the disease in the systemic lymph nodes with extensive skin rashes. The patient repeats recurrence and PR several times and still continues the inhalation therapy with other combination chemotherapy.

Case 9 (47 years old, female; acute type)

This patient was referred to out hospital from her community hospital. She had been admitted at the hospital because of pain in the knee and foot joints, which was more evident on gait. During evaluation she was found to have multiple osteolytic lesions and ATL cells on a film of the peripheral blood. A diagnosis of ATL was made and she was referred.

The IFN- γ inhalation therapy was started on with the combination chemotherapy without noticeable improvement.

Case 10 (55 years old, female; lymphoma type).

This patient was first admitted to our hospital with enlargement of submandibular, axillary and inguinal lymph nodes, the largest measuring 4.0cm in diameter. Five weeks prior to her admission she had noticed a swelling on the left side of her submaxillary nodes. A biopsy of a inguinal node showed malignant lymphoma, diffuse, medium-sized cell type (T-cell type with markers of CD3, CD11 and CD25).

After diagnosis of ATL she started to receive the IFN- γ inhalation therapy with the combination chemotherapy. Two weeks after the treatment, almost all the lymph nodes swelling had disappeared, but 1 to 3 % of abnormal lymphoid cells (ATL-like cells) were seen on peripheral blood smears. She continued the inhalation therapy 3 times a week at her home, but 33 weeks after the treatment she developed recurrence of the disease in the neck. She was admitted again, and received the IFN- γ inhalation therapy twice-a-day with other combination chemotherapy with remarkable effect, and was discharged from out hospital in condition of PR. Now she continues the inhalation every day at her home.

Case 11 (49 years old, female; lymphoma type)

This patient was referred to out hospital because of skin rashes, cough, dyspnea, fever up, ATL cells on the examination of blood smear and extensive reticulo-granular shadows in the bilateral lung field in chest Xp view.

As a diagnosis of ATL she started to receive the IFN- γ inhalation therapy with ordinaly conservative treatment including antibiotics. All the symptoms improved gradually by the treatment for 3 months, but lymph nodes swelling appeared in the neck. Histological examination of the specimen obtained by lymph node biopsy revealed malignant lymphoma, diffuse, medium-sized cell type (T-cell type with markers of CD4 and CD25). An additional combination chemotherapy was given with poor effect. She died due to sepsis 5 months after the treatment.

Case 12 (41 years old, male; lymphoma type)

This patient had been in his usual state of good health until 1 month prior to admission to his community hospital, when he noticed right cervical lymph nodes enlargement. At his community hospital, histological examination of the specimen obtained by right cervical lymph node biopsy revealed malignant lymphoma, diffuse, pleomorphic type (T-cell type with markers of CD3 and CD25), and chest Xp showed bilateral hilar lymph nodes swelling. Four weeks later, he was referred to our hospital for the treatment. The combination treatment of IFN- γ inhalation and chemotherapy was given successfully, and one month after

the therapy, almost all symptoms disappeared. he continues to receive the same treatment at outpatients clinic. No evidence of recurrence is seen.

TABLE 1

Case No.	Risk	Conditions before treatment			Total dose of IFN- γ , $\times 10^6$ JRU	Effect and duration of effect		Side effects
		Performance status	WBC (ATL cell %)	Chemotherapy		Effect	Duration (weeks)	
1	M	1	8,800 (44.0%)	-	201	PR	16 +	Mild fever
2	L	0	8,700 (14.0%)	-	144	NC	12 +	-
3	L	1	12,300 (38.0%)	-	186	NC	12 +	Mild fever
4	M	0	6,700 (45.5%)	-	108	PR	4 +	-
5	H	4	3,600 (22.0%)	+	237	PR	10 +	Mild fever
6	H	3	6,900 (9.0%)	+	66	PD	-	-
Remarks) Performance status (PS) was graded based on the criteria set by WHO. Risk was classified into the following groups by the standard set by the Malignant Lymphoma Study Group: L: Low risk; M: Moderate risk; and H: High risk (J. Clin. oncol., Vol. 6, No. 7 1088-1097 (1988)).								

TABLE 2

Case No.	Risk	Conditions before treatment			Total dose of IFN- γ , $\times 10^6$ JRU	Effect and duration of effect		Side effects
		Performance status	WBC (ATL cell %)	Chemotherapy		Effect	Duration (weeks)	
7	M	1	12,800 (30.0%)	-	777	PR	34 +	-
8	H	1	9,300 (23.5%)	-	660	PR	6	-
9	L	1	4,100 (22.0%)	-	120	NC	10	-
10	H	2	6,500 (0.0%)	-	540	PR	31	-
11	H	4	8,300 (8.0%)	-	315	PD	-	-
12	M	0	12,800 (0.0%)	-	441	PD	19 +	-
Remarks) Performance status (PS) was graded based on the criteria set by WHO. Risk was classified into the following groups by the standard set by the Malignant Lymphoma Study Group: L: Low risk; M: Moderate risk; and H: High risk (J. Clin. oncol., Vol. 6, No. 7 1088-1097 (1988)).								

(Conclusion)

As compared with the conventional systemic administration of IFN- γ , this method of treatment is a more effective method, with very slight side effects. This method of treatment is considered to be useful not only for the treatment of ATL, but also widely for malignant tumors, refractory infections and AIDS.

Claims

1. A method for the treatment of ATL, comprising administering an effective amount of interferon- γ to a mammalian species in need of such treatment *via* respiratory tract by inhalation.

2. The method claimed in Claim 1, wherein 1,000,000 JRU to 6,000,000 JRU of said interferon- γ is repeated at twice-a-day to weekly intervals.

3. The method claimed in Claim 2, said interferon- γ is of human.

4. The method claimed in any one of Claims 1 to 3, said interferon- γ is recombinant one.

5. The method claimed in Claim 1 or 2, comprising nebulizing an aqueous solution or suspension of said interferon- γ in the use for inhalation.

6. The method claimed in Claim 1 or 2, comprising being combined with the other known therapy for the disease.

7. An inhalant for the treatment of ATL, comprising containing interferon- γ .

8. The inhalant claimed in Claim 7, being useful for the method characterized by the administration of an effective amount of interferon- γ to a mammalian species in need of such treatment *via* respiratory tract by inhalation.

9. The inhalant claimed in Claim 7 or 8, said interferon- γ is recombinant.

10. The inhalant claimed in Claim 7, further containing serum albumin.

11. The inhalant claimed in Claim 8 or 9, comprising said interferon- γ , serum albumin, maltose, and an agent capable of buffering the resulting solution in a pH range between 6.5 and 7.5 when dissolved in distilled water or physiological saline.

12. The inhalant claimed in Claim 10 or 11, being useful for the method described in any one of the Claims 1 to 6.

13. A use of interferon- γ or the composition containing the same for the manufacture of a medicament for the application to a mammalian species suffering from ATL, which is characterized in that an effective amount of interferon- γ is administered *via* respiratory tract by inhalation to the subject in need of such treatment.

14. The use claimed in Claim 13, characterized in that 1,000,000 JRU to 6,000,000 JRU of said interferon- γ is repeatedly administered to human adults at twice-a-day to weekly intervals.

Claims for the following Contracting States: ES, GR

1. A method for preparing a pharmaceutical composition for the administration via the respiratory tract by inhalation containing interferon- γ (IFN- γ), which comprises combining an effective amount of IFN- γ with a physiologically acceptable vehicle for inhalation.

2. The method of claim 1 wherein a single dose of IFN- γ is about 1,000,000 to 6,000,000 JRU.

3. The method of claim 2 wherein a single dose of IFN- γ is about 3,000,000 JRU.

4. The method of any one of claims 1-3 wherein the IFN- γ is human.

5. The method of any of claims 1-4 wherein the IFN- γ is produced by recombinant DNA technology.

6. The method of any one of claims 1-5 wherein the administration by inhalation is performed by nebulizing an aqueous solution or suspension of said IFN- γ .

7. The method of any one of claims 1-6 wherein additionally serum albumin is used.

8. The method of any one of claims 1-7 wherein additionally maltose and a buffer capable of maintaining the pH in a range of 6.5 to 7.5 in distilled water or physiological saline are used.

9. The method of any one of claims 1-10 wherein the obtained composition is used for the treatment of adult T cell leukemia/lymphoma (ATL).

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PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 8)
A,P	MEDLINE ABSTRACT no.90065143; J.NAKAYAMA et al.: "Cutaneous lesion of adult T-cell lymphoma treated successfully with local hyperthermia in combination with intravenous administration of rINF-gamma"; & NIPPON HIFUKA GAKKAI ZASSHI, July 1989, vol.99,no.8, pages 907 - 914	7-13	A61K37/66
A	BIOLOGICAL ABSTRACT no.83120094; K.TAMURA et al.: "Recombinant interferon beta and gamma in the treatment of adult T-cell leukemia"; & CANCER, vol. 59, no.6, 1987, pages 1059 - 1062	7-13	
A	EPA 0276120 (SCHERING) * the whole document *	7-13	
A,P	USA 4851219 (SHERWIN S.A.) * the whole document *	7-13	TECHNICAL FIELDS SEARCHED (Int. Cl. 8)
	.../2		A61K37/66
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 7 - 13</p> <p>Claims searched incompletely:</p> <p>Claims not searched: 1 - 6, 14</p> <p>Reason for the limitation of the search:</p> <p>Method for treatment of the human or animal body by therapy. Article 52 (4) EPC</p>			
Place of search BERLIN		Date of completion of the search 10.08.1990	Examiner P. AVEDIKIAN
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p> <p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A,P	WOA 8903224 (ROUSSEL UCLAF) * the whole document *	7-13	
A	WOA 8806891 (AKTEBIOLAGET ASTRA) * the whole document *	7-13	
			TECHNICAL FIELDS SEARCHED (Int. Cl.)